EXHIBIT 18

2248/43966-CABPCT-US JPW/BJA

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Office Action Summary

Application No.	Applicant(s)	
11/259,540	ALLAWAY ET AL.	
Examiner	**Art Unit**	
Jeffrey S. Parkin	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 03 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Appeal Brief Resp. Due: 4/27/09
4mo - 5/27/09
5mo - 6/27/09
6mo - 7/27/09

Status Report - JA - 02/10/09

1)☒ Responsive to communication(s) filed on *29 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-15* is/are pending in the application.

4a) Of the above claim(s) *7,14 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/29/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Applicants: Graham P. Allaway et al.
Serial No.: 09/888,938
Filed: June 25, 2001
Exhibit 18

Detailed Office Action

Status of the Claims

Acknowledgement is hereby made of receipt and entry of the communication filed 29 September, 2008, wherein claims 8 and 13 were amended. Claims 7-15 are pending in the instant application. Claims 7, 14, and 15 stand withdrawn from further consideration while claims 8-13 are currently under examination.

37 C.F.R. § 1.98

The information disclosure statement filed 29 September, 2008, has been placed in the application file and the information referred to therein has been considered.

35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-13 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Two separate requirements are set forth under this statute: (1) the claims must set forth the subject matter that applicants regard as their invention; and (2) the claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant. Applicants' claim amendments are

noted, however, they still raise issues of ambiguity. First, the reference to the various viral phenotypes is confusing. Although the claims reference a "T cell tropic HIV-1 isolate" or "macrophage-tropic HIV-1 isolate", these terms still remain ambiguous. It is not readily manifest if the claims are directed toward laboratory-adapted strains or primary isolates. The distinction is important because many primary T-cell tropic isolates are actually capable of replication in PBMCs (Valentin *et al.*, 1994; Simmons *et al.*, 1996). It would be less ambiguous to reference laboratory-adapted isolates or primary isolates, as well as, more details concerning their phenotype (i.e., syncytium-inducing/high replicative capability T-cell tropic isolates or non-sycytium-inducing/slow replicative capability macrophage-tropic isolates). Second, it is not readily manifest what is being administered to the cell. For instance, are HIV-1 virions being added to the cell? Are HIV-1-infected cell lines being added? Are viral pseudotypes expressing the HIV-1 Env being examined? Applicants should clearly and unambiguously identify the source of the viral Env. Third, the claimed methodology fails to clearly set forth the phenotype of the target cell. What is the genotype/phenotype of the "first" $CD4^+$ cell? What is the genotype/phenotype of the "second" $CD4^+$ cell target? Alternatively, are non-$CD4^+$ cell lines that have been transfected with CD4/coreceptor-expressing plasmids been employed? It is imperative that the precise characteristics of the cell lines be set forth, especially considering the genotypic/phenotypic characteristics of various HIV-1 isolates. Appropriate correction as supported by the disclosure is required.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 8-13 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are directed toward a method of determining whether an HIV-1 "test" isolate is T-cell tropic. However, the methods as currently claimed are defective and do not enable the skilled artisan to accurately assess the tropism of any given "test" isolate. The legal considerations that govern enablement determinations pertaining to undue experimentation have been clearly set forth. *Enzo Biochem, Inc.*, 52 U.S.P.Q.2d 1129 (C.A.F.C. 1999). *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988). *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance

presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The disclosure fails to provide adequate guidance pertaining to the use of the terms "T cell tropic HIV-1 isolate" or "macrophage-tropic HIV-1 isolate". It is not readily manifest if the claims are directed toward laboratory-adapted strains or primary isolates. The distinction is important because many primary T-cell tropic isolates are actually capable of replication in PBMCs (Valentin *et al.*, 1994; Simmons *et al.*, 1996). It would be less confusing to reference laboratory-adapted isolates or primary isolates, as well as, more details concerning their phenotype (i.e., syncytium-inducing/high replicative capability T-cell tropic isolates or non-sycytium-inducing/slow replicative capability macrophage-tropic isolates).

2) The disclosure fails to provide adequate guidance pertaining to the nature of the "Env" that is being administered. For instance, are HIV-1 virions being added to the cell? Are HIV-1-infected cell lines being added? Are viral pseudotypes expressing the HIV-1 Env being examined? It is imperative that the skilled artisan understand the source of the viral Env in order to practice the claimed invention.

3) The disclosure fails to provide adequate guidance pertaining to the phenotype of the target cell. What is the genotype/phenotype of the "first" $CD4^+$ cell? What is the

genotype/phenotype of the "second" $CD4^+$ cell target? Alternatively, are non-$CD4^+$ cell lines that have been transfected with CD4/coreceptor-expressing plasmids been employed? It is imperative that the precise characteristics of the cell lines be set forth, especially considering the genotypic/phenotypic characteristics of various HIV-1 isolates.

4) The disclosure fails to provide any working embodiments involving the claimed methodology. This is not surprising since the method steps are defective.

5) The methodology steps, as presently constructed, are inherently flawed and do not enable the skilled artisan to accurately assess the phenotype of any given isolate. For instance, Velentin *et al.* (1994) reported (see abstract, p. 6684) that "isolates with a rapid/high syncytium-inducing phenotype did not differ from slow/low, non-syncytium-inducing isolates in their ability to replicate in monocyte-derived macrophages." In other words, this study demonstrated that HIV-1 isolates can infect **both** mononuclear phagocytes and lymphocytes, irrespective of their biological phenotype and passage history. Simmons *et al.* (1996) also noted that primary SI strains (or T-cell tropic strains) replicated efficiently in both T-cell lines (e.g., C8166) and blood-derived macrophages. The authors concluded that these isolates were dual-tropic and replicated far more efficiently than laboratory-adapted T-cell tropic isolates.

Accordingly when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

Nonstatutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 U.S.P.Q.2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 U.S.P.Q.2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 U.S.P.Q. 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 U.S.P.Q. 761 (C.C.P.A. 1982); *In re Vogel*, 422 F.2d 438, 164 U.S.P.Q. 619 (C.C.P.A. 1970); and *In re Thorington*, 418 F.2d 528, 163 U.S.P.Q. 644 (C.C.P.A. 1969). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) or § 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. § 3.73(b).

The previous rejection of claims 8-13 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 6,261,763, is hereby withdrawn in response to Applicants' submission of a terminal disclaimer.

Action Is Final, Necessitated by Amendment

Applicantss amendment necessitated any and all new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a). A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. § 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 10:30 AM to 9:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Bruce R. Campell, Ph.D., can be reached at (571) 272-0974. Direct general status inquiries to the Technology Center 1600

receptionist at (571) 272-1600. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Applicants are reminded that the United States Patent and Trademark Office (Office) requires most patent related correspondence to be: a) faxed to the Central FAX number (571-273-8300) (updated as of July 15, 2005), b) hand carried or delivered to the Customer Service Window (now located at the Randolph Building, 401 Dulany Street, Alexandria, VA 22314), c) mailed to the mailing address set forth in 37 C.F.R. § 1.1 (e.g., P.O. Box 1450, Alexandria, VA 22313-1450), or d) transmitted to the Office using the Office's Electronic Filing System. This notice replaces all prior Office notices specifying a specific fax number or hand carry address for certain patent related correspondence. For further information refer to the Updated Notice of Centralized Delivery and Facsimile Transmission Policy for Patent Related Correspondence, and Exceptions Thereto, 1292 Off. Gaz. Pat. Office 186 (March 29, 2005).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,

/Jeffrey S. Parkin/

Jeffrey S. Parkin, Ph.D.
Primary Examiner
Art Unit 1648

21 January, 2009

Notice of References Cited	Application/Control No. 11/259,540	Applicant(s)/Patent Under Reexamination ALLAWAY ET AL.	
	Examiner Jeffrey S. Parkin	Art Unit 1648	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
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	I	US-			
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FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Valentin, A., et al., 1994, Dual tropism fo rmacrophages and lymphocytes is a common feature of primary human immunodeficiency virus type 1 and 2 isolates, J. Virol. 68(10): 6684-6689.
	V	Simmons, G., et al., 1996, Primary, syncytium-inducing human immunodeficiency virus type 1 isolates are dual-tropic and most can use either Lestr or CCR5 as coreceptors for virus entry, J. Virol. 70(12):8355-8360.
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/259,540	10/25/2005	Graham P. Allaway	2048/43966-CAB-PCT-US/JPW	5014

23432 7590 01/27/2009

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01/27/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.